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The role of phosphorus restriction in the prevention of secondary hyperparathyroidism in chronic renal disease

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In normal man, the serum phosphate concentration is maintained within a narrow range, despite random and spontaneous variations in phosphorus ingestion. On an average diet in the United States, the intake of elemental phosphorus approximates one gram per day. Of this amount, about 30% is excreted through the gastrointestinal tract and 70%, or about 700 mg/day, is excreted by the kidneys. To effect this rate of excretion with a normal glomerular filtration rate (GFR), some 15% of the filtered load of phosphate must be excreted; the tubular reabsorption of phosphate (TRP) thus is equal to about 85% of the filtered load. The absolute value for TRP will vary depending upon the amount of phosphate requiring excretion, and the primary effector element in the control system which governs phosphate homeostasis appears to be parathyroid hormone (PTH). Most studies indicate that the modulation of tubular reabsorption of phosphate takes place in the proximal tubule [1–3], although some investigators have presented evidence suggesting distal participation in phosphate reabsorption [4, 5].

In chronic renal disease, the control system responsible for the maintenance of external phosphate balance is perturbed progressively by virtue of the continuing loss of excretory units. As GFR falls, an adaptation takes place in phosphate excretion which is characterized by a progressive decrease in TRP, and thus by an increase in the rate of phosphaturia per residual nephron. This adaptation is sufficiently precise to permit the maintenance of normal serum phosphate concentrations on an unrestricted phosphorus intake until relatively late in the course of advancing chronic renal disease. We have demonstrated that PTH plays a key role in mediating the increasing rate of phosphate excretion per nephron, and that when PTH release is suppressed, either by sustained elevation of the serum calcium concentration or by surgical removal of the parathyroid glands, the augmented degree of phosphaturia per nephron is reversed [6–8]. The role of PTH in the regulation of external phosphate balance in advancing renal disease is particularly important during the decline of GFR from normal to approximately 25% of normal. However, once the blood concentration of PTH exceeds the level at which maximal inhibition of the tubular reabsorption of phosphate is to be expected, other factors, including a rising concentration of serum phosphate (and thus an increase in the filtered load of phosphate per residual nephron) and possibly factors that inhibit proximal tubular sodium reabsorption, must contribute to the regulation of phosphate balance.

In examining the events which initiate the adaptation in phosphate excretion in chronic renal disease, we recently have focused attention on the role of the phosphate ion per se. Although it is known that phosphate does not itself affect the release of parathyroid hormone [9], a close relationship exists between phosphate and calcium metabolism, and changes in ionized calcium concentrations clearly influence the rate of parathyroid hormone release [10, 11]. The possibility thus exists that primary and repetitive changes in phosphate excretion attendant upon the loss of nephrons and the fall in GFR could lead to closely coupled changes in the concentration of ionized calcium in the serum. In normal volunteers, it recently has been shown that an increase in serum phosphate concentration, induced by the administration of an oral phosphate load, is associated with a reciprocal change in ionized calcium and a rise in the level of serum parathyroid hormone [12].

The specific hypothesis which we have proposed for the pathogenesis of secondary hyperparathyroidism is as follows [13]: During the evolution of chronic renal disease, recurrent but transient periods of phosphate retention must occur each time GFR falls, for there will be a temporary decrease in phosphate excretion, and if the intake and

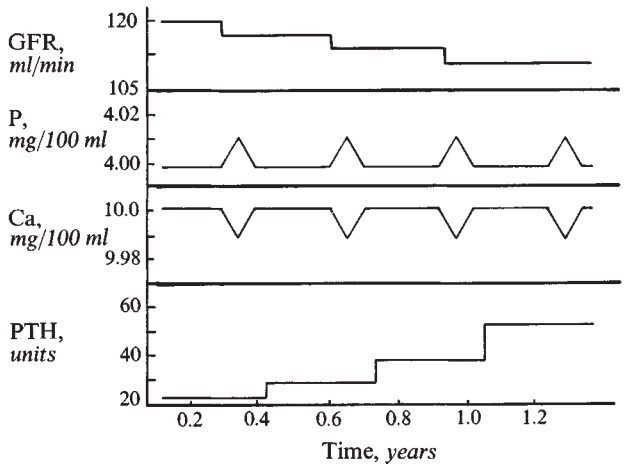

Fig. 1. *Hypothetical treatment for the pathogenesis of secondary hyperparathyroidism in advancing chronic renal disease.* (From [13].)

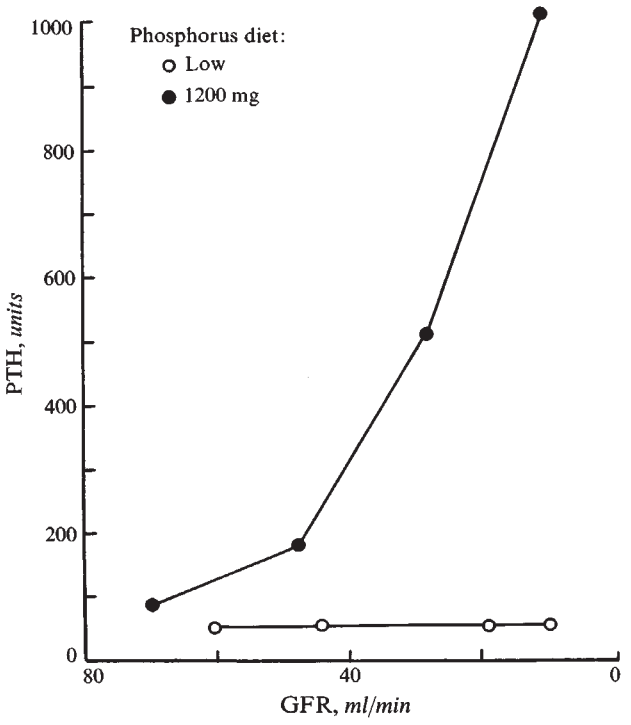

Fig. 2. *The relationship between parathyroid hormone levels and GFR in two groups of dogs.* One group (closed circles) was maintained on a diet containing 1,200 mg of phosphorus per day. The other group (open circles) was maintained on a diet containing less than 100 mg of phosphorus per day. PTH is expressed in microliter equivalents per ml. (From [14].)

absorption of phosphorus remain constant positive balance must ensue. The phosphorus retention, even though it may be very small in magnitude, will lead to an increase in plasma phosphate concentration; and the latter, it is proposed, will produce a reciprocal decrease in the serum calcium concentration. The fall in ionized calcium would be sensed by the parathyroid glands which respond by increasing the rate of parathyroid hormone secretion. Finally, the increase in the level of PTH in the blood perfusing the kidneys, will serve to diminish the rate of TRP and thereby promote a greater rate of phosphaturia per remaining nephron. Thus, total phosphate excretion will rise and the serum phosphate concentration will return to normal. The elevated PTH level will also serve to increase the serum calcium concentration by the action of this hormone on bone and the gastrointestinal tract. With each phase of nephron destruction, the same cycle should recur; therefore, the levels of PTH should increase progressively as the degree of renal insufficiency increases. This hypothesis, which is depicted schematically in Fig. 1, has been subjected to experimental examination in dogs with progressive renal insufficiency [14].

Studies were performed on two groups of dogs. The first group was fed a diet containing 1,200 mg of phosphorus per day. The second group received a low phosphorus diet containing less than 100 mg of phosphorus per day. Control studies were performed with both kidneys intact; then approximately 70 to 80% of the right kidney was infarcted by ligating most of the branches of the right renal artery. After a period of seven to ten days, a second set of studies was performed and a similar surgical procedure was performed on the left kidney. One week to ten days later, the third set of studies was performed. The left kidney was then removed, leaving only the nephrons in the small remnant kidney on the right side. The fourth set of studies then was obtained. With this experimental approach, the GFR was reduced in graded steps from a mean of approximately 60 ml/min to 40, 20, and then to roughly 10 ml/min.

Fig. 2 depicts the levels of serum PTH in the two groups of dogs. Those animals maintained on 1,200 mg of phosphorus per day developed progressive secondary hyperparathyroidism. In contrast, the dogs fed the low phosphorus intake exhibited no increase in PTH levels, despite the development of advanced renal insufficiency. The results of these experiments clearly demonstrate that, at least for the duration of the studies, secondary hyperparathyroidism can be prevented by phosphate deprivation as GFR falls from normal to very low levels.

The effects of administering a single load of phosphorus to a uremic dog in the low phosphorus intake group are shown in Fig. 3. After baseline measurements were obtained, 600 mg of phosphorus were fed by gastric tube and observations were continued for 5 hr. The plasma phosphate concentration rose by approximately 3 mg/100 ml. The serum calcium fell reciprocally, reaching a minimum value approximately 1 mg/100 ml below the baseline values three hours after the phosphorus load. The serum PTH level rose by six-fold and the TRP, which originally was 98%, decreased in a remarkable fashion to zero at the end of five hours. These data demonstrate in a dramatic form

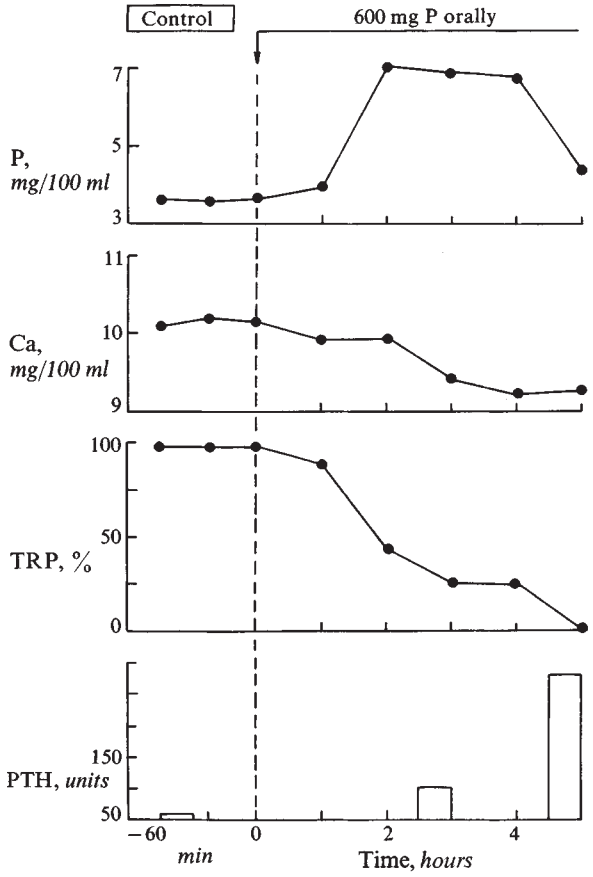

Fig. 3. *The effect of a single oral dose of 600 mg of phosphorus on serum phosphorus, calcium, TRP and parathyroid hormone levels in a uremic dog maintained chronically on a low phosphorus diet.* (From [14].)

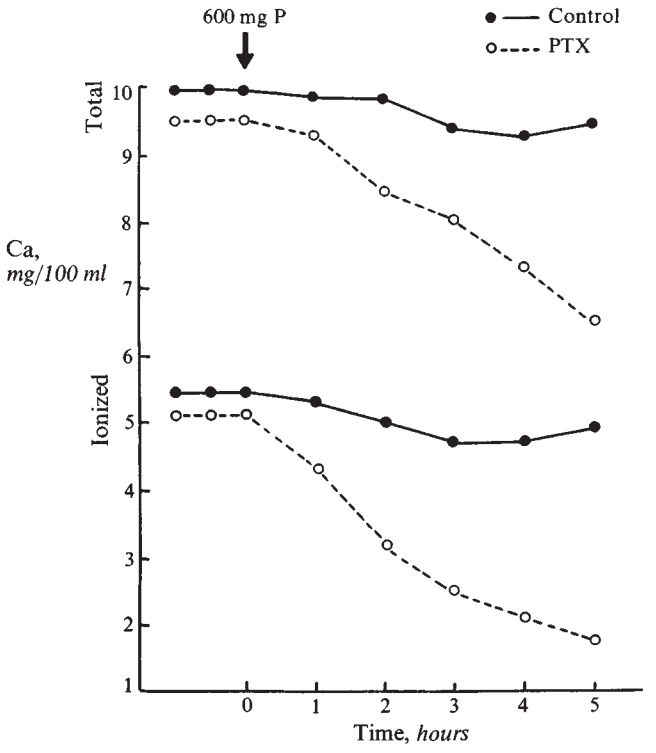

Fig. 4. *The effects of a single oral dose of 600 mg of phosphorus on total and ionized serum calcium concentrations in the same dog shown in Fig. 3 after total thyroparathyroidectomy.* (SLATOPOLSKY E, et al: Proceedings of the 5th Internat. Congress of Nephrology, Mexico, 1972. In Press.)

a sequence of events triggered by the addition of phosphorus to body fluids in a setting wherein the phosphate control system seemed to be hyper-responsive. The apparent order of events was as follows: phosphorus ingestion → elevation of serum phosphate concentration → reciprocal fall in calcium concentration → increase in serum PTH → inhibition of TRP → increased phosphate excretion per nephron. The fall in the serum calcium concentration in this experiment presumably was attenuated by the marked rise in the serum PTH levels; for when the same load of phosphorus was administered to the same dog after a total thyroparathyroidectomy, the decrease in both total and ionized serum calcium concentrations was strikingly greater (Fig. 4).

A role of phosphorus in the genesis of secondary hyperparathyroidism thus seems clearly implicated. However, the use of a very low phosphorus diet to prevent the development of hyperparathyroidism in advancing renal disease would be impractical, clinically, since it would require either severe limitation of protein intake and/or the administration of large doses of phosphate binding gels, starting early in the course of renal disease. Moreover, if a low phosphorus diet were to be maintained for months to years, phosphorus depletion and demineralization of the skeleton might well occur. Under these circumstances, one would simply substitute one pathologic condition, osteomalacia, for another, hyperparathyroidism.

In the hope of developing a regimen with clinical applicability and, simultaneously, to provide a more rigorous test of the validity of the hypothesis for the pathogenesis of secondary hyperparathyroidism, a different experimental protocol was devised [15]. If, during the evolution of renal failure, the load of phosphorus to be excreted by the kidneys could be decreased in proportion to the decrement in GFR, the adaptive increase in phosphate excretion per nephron would not be required and hyperparathyroidism should not occur. Specifically, if the transient periods of phosphorus retention were avoided, there would be no peaks in serum phosphorus concentration, no reciprocal changes in ionized calcium concentration, and parathyroid hormone levels should not rise progressively. A series of experiments, therefore, was performed on a group of dogs in which renal mass again was decreased in sequential steps, and, during the control phase, phosphorus intake was maintained at 1,200 mg/day. However, each time the nephron population was reduced, GFR was remeasured and the phosphorus intake was decreased by the same percentage as the fall in

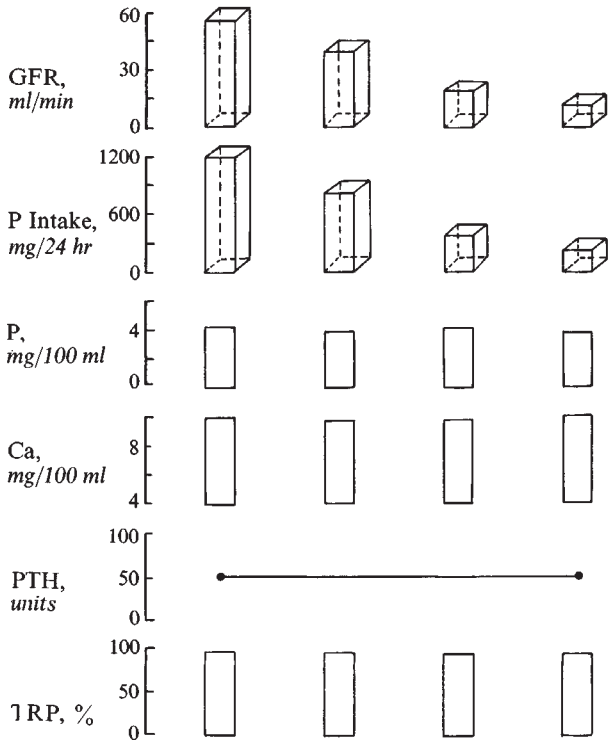

Fig. 5. *The effects of "proportional reduction" of phosphorus intake on the pathogenesis of secondary hyperparathyroidism.* (This figure was constructed from tabular data published in reference [15].)

GFR. The results of "proportional reduction" of phosphorus are shown in Fig. 5. No change in the levels of serum phosphorus or calcium were detected throughout the period of study. More critically, the TRP never fell below 85%, and the serum concentration of PTH remained normal even at the lowest levels of GFR.

During the evolution of chronic renal disease, if phosphorus intake remains constant, the maintenance of phosphorus balance and the simultaneous prevention of hyperphosphatemia until GFR falls to quite low values, occur because fractional excretion of phosphorus increases progressively in the surviving nephrons. PTH seems to be the main modulator of this adaptive increase. Unfortunately, the "trade-off" for the adaptation may be the development of metabolic bone disease [16]. The studies in which a low phosphorus diet was employed in dogs with experimentally induced renal insufficiency demonstrate that secondary hyperparathyroidism can be prevented. However, this regimen imposes the risk of phosphate depletion and osteomalacia. On the other hand, the use of "proportional reduction" of phosphorus in the diet should obviate the need for an adaptive increase in phosphate excretion per nephron without imposing the risk of phosphate depletion. This approach to the prevention of secondary hyperparathyroidism thus would seem to have clinical applicability. After GFR is measured, phosphorus intake can readily be reduced in the diet in proportion to the decrement in GFR if renal function is not too severely impaired. Preliminary studies in patients with chronic renal failure and GFR as low as 30 ml/min, indicate that secondary hyperparathyroidism can be reversed by diminishing dietary phosphorus intake. If the GFR is below 30 ml/min, the task of preparing a suitably low phosphorus diet becomes difficult. However, phosphate binding agents, such as aluminum carbonate gel or aluminum hydroxide gel, may be used in order to diminish phosphorus absorption by the gastrointestinal tract. It should be emphasised that the kidney is the only organ responsible for the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol [17, 18], the most potent metabolite of vitamin D. Patients with severe renal disease are unable to form this important metabolite; thus, "proportional reduction" of phosphorus intake will not eliminate any increase in PTH release which results from the development of vitamin D resistance; for once the latter abnormality is of sufficient severity to impair the enteric absorption of calcium, a separate mechanism may exist for decreasing the serum ionized calcium concentration, and thus for provoking secondary hyperparathyroidism. If vitamin D resistance ultimately is shown to contribute importantly to one or more of the component parts of uremic osteodystrophy, it will become essential to add one of the potent metabolites of vitamin D to the therapeutic regimen. However, before this is done, any preexisting hyperphosphatemia must be corrected in order to prevent the development of metastatic calcification.

In summary, we believe that a basis now exists for a prospective approach to the prevention of secondary hyperparathyroidism, and probably other forms of metabolic bone disease, in advancing chronic renal disease. To date, controlled studies have been performed only on dogs with experimental renal disease; however, preliminary results in patients are encouraging and long-term clinical studies must now be undertaken.

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